REMARKS

Claims 49-52, 54-65, and 68 are pending and are rejected under 35 U.S.C. § 103 and are provisionally rejected for nonstatutory obviousness-type double patenting. Claims 49 and 51 are amended. Each of the rejections is addressed below.

Support for the Amendment

Support for the amendments is found throughout the specification and claims as originally filed. In particular, support for the amendment of claim 49, which now recites that the "method improves said cardiac function" is found, for example, at page 58, lines 4 and 5; support for the amendment of claim 51, which now recites "VEGF-B, VEGF-C, VEGF-2, and VEGF-3" is found, for example, at page 21, lines 25 and 26.

Rejection under 35 U.S.C. § 103(a)

The Office rejects claims 49-52, 54-65, and 68, which are directed to methods for inducing new blood vessel growth in myocardial tissue, under 35 U.S.C. § 103(a) as obvious over International Publication No. WO 97/14307 by Isner et al., (hereinafter "Isner") in view of U.S. Patent No. 5,880,090, to Hammond et al. (hereinafter "Hammond"), and U.S. Patent No. 6,605,274 to Dillman et al., (hereinafter "Dillman"). For the reasons detailed below, Applicants respectfully disagree with the rejection and request that it be withdrawn.

Legal Standard for Obviousness

The test of obviousness *vel non* is statutory. It requires that one compare the claim's "subject matter as a whole" with the prior art "to which said subject matter pertains." 35 U.S.C. §103(a). The inquiry is fact-specific and must include i) the scope and content of the prior art; ii) the differences present between the prior art and the claimed invention; iii) the level of ordinary skill in the art at the time of filing; and iv) objective evidence of non-obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 149 USPQ 159, 467, 86 S. Ct. 684 (1966). Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. *In re Fine*, 837 F.2d

1071,1075, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). To prevent the use of hindsight based on the invention to defeat patentability, the Federal Circuit requires the Examiner to show a motivation to combine the references that create the case of obviousness. *In re Roufett*, 149 F.3d 1350, 1357, 47 U.S.P.Q.2d 1453, 1457-1458 (Fed. Cir. 1998). The Examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed. *Id.* When the references cited by the Patent Office fail to establish a *prima facie* case of obviousness, the rejection is improper and must be withdrawn. *In* re Fine, 837 F.2d at 1074, 5 U.S.P.Q.2d at 1598.

Isner

The Examiner has considered the scope and content of Isner and acknowledged that differences exist between the prior art and the claimed invention. In particular, the Examiner asserts that Applicants' claimed invention differs from that of Isner because Isner fails to teach methods for monitoring cardiac function. The Examiner states: "Isner also does not teach specifically to monitor a cardiac function by one of the recited approaches." (Office action p. 5, lines 16 and 17; emphasis present in the original.)

As acknowledged by the Examiner, Applicants' claims recite monitoring a cardiac function by echocardiography, ventricular end-diastolic dimension (LVEDD), end-systolic dimension (LVESD), fractional shortening (FS), wall motion score index (WMSI), electromechanical mapping, cardiac angiography or LV systolic pressure (LVSP). The Examiner indicates that this feature distinguishes Applicants' claimed invention from Isner.

To further emphasize the differences between Applicants' claimed invention and the cited prior art references, Applicants claims now recite "wherein the method improves said cardiac function." Applicants specifically describe results showing that a combination of gene transfer and cytokine treatment improves cardiac function as measured by echocardiographic fractional shortening and regional wall motion score (Applicant's specification, page 56, lines 6-19). Applicants state that "in chronic MI [myocardial infarction] combo therapy resulted in **superior improvement** in all indices of perfusion and function compared to all other treatment groups." (Applicants specification, page 58, olines 4 and 5)

To remedy the alleged deficiency in Isner identified by the Examiner, the Examiner cites Dillman.

Dillmann

Dillmann describes methods for monitoring the function of a cardiac tissue. The Examiner asserts that it would be obvious for the skilled artisan to monitor the effects of the treatment described by Isner by monitoring cardiac function using the methods described by Dillmann. Applicants respectfully disagree. As discussed above, in order to establish a prima facie case of obviousness, the Federal Circuit requires the Examiner to show some motivation to combine the references that create the case of obviousness. *In re Roufett*, 149 F.3d 1350, 1357, 47 U.S.P.Q.2d 1453, 1457-1458 (Fed. Cir. 1998). A teaching, suggestion, or motivation to combine cannot be merely derived from the fact that the combination could be made, rather the motivation "must be clear and particular." *In re Dembiczak*, 175 F.3d 994, 50 USPQ 2d 1614 (Fed. Circ. 1999). The Federal Circuit cautions against inferring the presence of such motivation where it lacks this particularity. The Court states:

> Instead, in complex scientific fields, the Board could routinely identify the prior art elements in an application, invoke the lofty level of skill, and rest its case for rejection. To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness.

In sum, it is not sufficient to show that Applicants' claimed combination *could* be made. Rather, the Examiner must show some particular teaching or suggestion within the references themselves that the combination ***should*** be made.

Hammond

The Examiner cites Hammond as disclosing the use of stem cell factor and granulocyte macrophage colony stimulating factor for the mobilization of endothelial cell progenitors. Applicants note that the use of such factors is recited only in claims 58 and 68.

Hammond differs from Applicants claimed invention because Hammond describes methods for coating a ***synthetic vascular graft*** with endothelial cells. Such methods are clearly different from the claimed invention which recites methods for inducing blood vessels in

myocardial tissue. First, the grafts described by Hammond are entirely synthetic and comprise polyethylene terephthalate and polytetrafluoroethylene. The usefulness of such grafts is limited by their tendency to promote clot formation (column 1, lines 15-26). To overcome such limitations, Hammond describes methods for increasing the number of endothelial cells that ***attach to and coat the surface*** of synthetic grafts (column 1, line 60, to column 2, line 5). Not only are such synthetic grafts plainly distinct from a myocardial tissue, but the process for forming an endothelial coating on such a graft is clearly different from the process required to generate new blood vessel within a tissue. Hammond teaches that endothelialization promoting agents (e.g., GM-CSF, G-CSF) enhance "**adherence of circulating endothelial cells to graft surfaces**, or may stimulate the multiplication of blood-borne endothelial precursors that have become **adhered**." (column 2, lines 64-67.) Hammond teaches that this process relies on "'fallout endothelialization.' More specifically, it has been proposed that the circulating cells give rise to endothelial coatings of vascular prostheses . . . " Methods for increasing the number of endothelial cells that adhere to and coat a synthetic graft are distinctly different from the multifaceted biological processes that regulate blood vessel formation within a myocardial tissue.

Applicants' specification teaches that the formation of blood vessels in a tissue involves the complex regulation of a variety of endothelial cell functions and activities, including cell migration, proliferation, the formation of endothelial cell sprouts, vascular loop formation, the development of capillary tubes and the subsequent formation of tight junctions and the deposition of new basement membranes (page 2, lines 10-15). Such vascular networks fulfill a critical biological function within the tissue of the subject by providing oxygen and nutrients and removing wastes (page 1, lines 27-30). Hammond's process of coating a synthetic graft with endothelial cells is plainly different from the process of blood vessel formation. Methods for increasing the number of endothelial cells that form an endothelial coating on a vascular prosthesis are distinctly different from Applicants' claimed methods, which provide for the formation of new blood vessels in a myocardial tissue. Hammond clearly fails to teach or suggest such methods.

The endothelialization results obtained by Hammond fail to provide the requisite motivation to combine or the expectation of success to modify the methods of Isner. A thorough reading of Hammond suggests that methods for promoting endothelialization may have undesired side effects that would dissuade the skilled artisan from utilizing the methods

described by Hammond. In particular, Applicants invite the Office's attention to Example 1, where Hammond describes grafts having endothelial coatings. Regarding such grafts, Hammond states,

> [T]he BMB grafts implanted for four weeks or longer appeared stiff. Histological studies revealed many **osteocytes with microcalcification in the outer graft wall** of these grafts, but not in the inner wall or intima, even at three months. **In the BMB grafts implanted longer than four weeks, osteoblasts, osteocytes, and microcalcifications were found. These undesirable side effects could affect the long-term utility of such grafts . . .** (column 7, lines 55-63)

Hammond's disclosure of adverse results associated with the endothelialization of grafts teaches away from the use of such methods. In view of this teaching away, one skilled in the art would lack the requisite motivation to introduce changes to the methods of Isner, and would further lack the expectation of success required to introduce such changes.

The Examiner asserts that *in vivo* studies failed to show these undesirable side-effects. Applicants respectfully disagree. Hammond merely states that two dogs that received synthetic grafts had 80% and 35% of their graft surfaces covered with endothelial like cells (Column 9, lines 48-50). This summary in Example 3 fails to indicate whether or not the grafts were evaluated for the presence of microcalcification. Furthermore, Example 4 fails to provide any description of results.

The Examiner asserts that Hammond describes the use of $CD34^+$ cells for the repair of ischemic tissue. Applicants respectfully disagree. In the cited passage, Hammond states that CD34+ cell populations derived from peripheral blood "include a subset of cells that are capable in culture of differentiating into endothelial-like cells." (Hammond, column 3, lines 28-37). Hammond further states that it was "**proposed** that these circulating $CD34^+$ or $Flk\text{-}1^+$ cells participate in the repair of ischemic tissue." This proposal based on an *in vitro* study is insufficient to provide the requisite expectation of success or motivation to combine.

In sum, Hammond fails to teach or suggest any method for inducing new blood vessel growth in a myocardial **tissue** of a mammal, much less Applicants' claimed methods, which recite administering an effective amount of a nucleic acid encoding at least one angiogenic protein, and administering an effective amount of at least one angiogenic factor, thereby inducing blood vessel growth in the myocardial tissue and increasing the frequency of

endothelial progenitor cells in the mammal. Moreover, one skilled in the art would lack the requisite expectation of success to combine the methods of increasing synthetic graft endothelialization described by Hammond with any other method described in the references cited by the Office to arrive at Applicants' claimed combination.

Applicants were the first to discover methods for inducing new blood vessel growth in a myocardial tissue of a mammal by administering an effective amount of a solution comprising a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof into the myocardial tissue; and administering to the mammal an effective amount of at least one angiogenic factor or an effective fragment thereof, thereby inducing new blood vessel growth in the myocardial tissue of the mammal, and increasing the frequency of endothelial progenitor cells (EPC) in the mammal. It is not sufficient that one ***could*** have made the combination, the cited references must suggest the ***desirability*** of making the claimed combination and must further indicate that the combination if made would have succeeded.

Applicants were the first to appreciate that blood vessel growth could be induced using such methods, and that the growth of such blood vessels would improve cardiac function. None of the references cited by the Office, alone or in any combination, teaches or suggests all of the claimed limitations of Applicants' claimed invention. The Office has failed to establish a *prima facie* case of obviousness, and for this reason alone the rejection of the claims under U.S.C. § 103(a) should be withdrawn.

Evidence of Unexpected Result

In their specification, Applicants describe methods of administering an effective amount of a nucleic acid encoding at least one angiogenic protein or an effective fragment thereof into the myocardial tissue and administering to the mammal an effective amount of at least one angiogenic factor or an effective fragment thereof to induce new blood vessel growth in myocardial tissue of the mammal and improve cardiac function. Applicants state that this combination is likely to provide a synergistic effect (page 7, line 27). As evidence that the combination is surprisingly effective, Applicants present data showing the effects of angiogenic gene therapy in combination with cytokine-induced endothelial progenitor cell mobilization in a swine model of chronic myocardial ischemia and a murine model of acute myocardial infarction

(pages 54-58). Applicants treated animals with chronic myocardial ischemia (swine) or with acute myocardial infarction with VEGF in combination with cytokines and measured the effect of this treatment on cardiac function. Applicants found that "In chronic MI [myocardial ischemia], **combo therapy resulted in superior improvement in all indexes of perfusion and function** compared with all other treatment groups." (page 58, lines 4 and 5). Moreover, Applicants disclose that the effect of cytokines in combination with VEGF was synergistic (page 58, lines 18 and 19).

None of the prior art references cited by the Examiner teach or suggest that combination therapy for the treatment of myocardial ischemia using would be so surprisingly effective. In particular, none teach that VEGF when administered with a cytokine would have a **synergistic** effect on cardiac function in ischemic myocardial tissues. Evidence of synergism is indicative of non-obviousness (*Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, U.S.P.Q. 2d 1181 (Fed. Cir. 1997). Moreover, where Applicants are able to show that the claimed invention is unexpectedly superior to the prior art, the unexpected results are sufficient to show that the invention is nonobvious.

> One way for a patent applicant to rebut a prima facie case of obviousness is to make a showing of "unexpected results," i.e., to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected. The basic principle behind this rule is straightforward—that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious. *In Re Pravin L. Soni* 54 F.2d 746 at 750; 34 U.S.P.Q.2d 1684 (Fed. Circ. 1995).

Furthermore, the mere presence of unexpected results is evidence that the claimed invention is nonobvious.

> Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice. There is always at least a possibility of **unexpected results, that would then provide an objective basis for showing that the invention, although apparently obvious, was in law nonobvious**. *In re Patrick H. O'Farrell*, 853 F.2d 894 at 903; 7 U.S.P.Q. 2d 1673 at (Fed Circ. 1988)

Applicants have provided evidence showing that the results obtained with the claimed invention are superior to what was expected based on the prior art. Accordingly, the obviousness rejection of the claims should be withdrawn.

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Double Patenting

Applicants acknowledge that claims 49-52, 54-65, and 68 are provisionally rejected over copending U.S. application No. 10/714,574. With regard to the provisional double patenting rejection over copending application No. 10/714,574, Applicants submit that upon consideration and entry of the instant Amendment and Response, the provisional double-patenting rejection will be the only rejection remaining in the instant application. Therefore, pursuant to M.P.E.P. § 822.01, Applicants respectfully request that the provisional obviousness-type double patent application be withdrawn so that the instant application may proceed to allowance.

CONCLUSION

In view of the above amendment and Remarks, Applicants believe the pending application is in condition for allowance. If the Examiner disagrees, Applicants respectfully request that the Examiner contact the undersigned agent by telephone to schedule an interview prior to the mailing of an Office action.

Applicants believe that no fee is due to consider the present amendment. Nevertheless, the Director is hereby authorized to charge or credit any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105.

Dated: December 26, 2006

Respectfully submitted,

By _____

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